Influence of preoperative cognitive status on propofol requirement to maintain hypnosis in the elderly

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Key points
- The effect of cognitive function on propofol requirement during anaesthesia is unclear.
- In this study, propofol target-controlled infusion was used to maintain BIS between 40 and 60 during anaesthesia in elderly patients.
- BMI and preoperative cognitive status had significant effect on propofol requirement.
- This is the first study to show that propofol requirements are reduced in elderly patients with cognitive dysfunction.

Background. The loss of cholinergic neurones in the basal forebrain has been shown to correlate to the extent of cognitive dysfunction during ageing in humans and to the hypnotic potency of propofol in animal models. We examined how the preoperative cognitive status, as assessed by mini-mental state examination (MMSE), may interact with propofol consumption during anaesthesia in the elderly.

Methods. In a prospective study, we recruited 41 patients (65–99 yr) undergoing surgery for hip fracture. Femoral nerve block was performed for analgesia. Target-controlled infusion of propofol (Schnider’s model) was adjusted to the bispectral index within the range 40–60. Multiple linear regression analysis determined whether age, BMI, gender, duration of anaesthesia, and preoperative MMSE score affected the propofol consumption (general linear model, Systat 8.0).

Results. BMI and MMSE score significantly affected the mean value of propofol consumption. A low MMSE score (below 19) was associated with an observed decrease in propofol requirement in patients.

Conclusions. Propofol requirement to maintain hypnosis during general anaesthesia appears to decrease with deterioration in the cognitive status in the elderly. We suggest that a cognitive dysfunction linked to a cerebral cholinergic dysfunction may influence the brain sensitivity for propofol in aged patients.

Keywords: acetylcholine; anaesthetics i.v.; cognition; elderly patients; MMSE; propofol

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Propofol has pharmacokinetic characteristics that allow for rapid onset and offset of the drug effect, and the use of target-controlled infusion (TCI) in elderly people. Different pharmacokinetic models have been developed for TCI; the Schnider pharmacokinetic model takes into account not only weight, gender, and height, but also the age to reflect modifications related to ageing. Such an approach has permitted a more precise therapeutic adjustment and a good cardiovascular tolerance to total i.v. anaesthesia in elderly subjects.

Indeed, hypnotic requirement decreases as age increases. This has been described with various anaesthetic agents such as isoflurane, sevoflurane, and propofol. Cognitive status, as an indicator of brain ageing, could per se modify the pharmacodynamics of propofol during anaesthesia and therefore modify the propofol requirement. To date, there is no available information on the interaction between cognitive status and propofol requirement during anaesthesia in humans.

The aim of this study was to determine whether or not the cognitive status influences the propofol requirement during TCI to maintain hypnosis during anaesthesia in elderly patients. For this purpose, we observed a population of patients undergoing hip fracture surgery and examined the influence of their preoperative mental state as assessed by the mini-mental state examination (MMSE) of Folstein and colleagues.

Methods
After individual informed consent and Ethics Committee approval, 41 patients, ASA II and III, aged 65–99 yr,
undergoing hip fracture surgery were included in this prospective, observational study (Table 1). Exclusion criteria were ASA > IV, high level of preoperative anxiety [Hamilton anxiety scale (HAMA) > 23], high level preoperative spontaneous pain (visual analogue pain scale > 4), severe cognitive impairment with no responses to anxiety and pain score assessment, or patients using anticholinergic drugs.

The characteristics of the 41 subjects are shown in Table 1. As shown in Figure 1, the consumption of propofol depended on the MMSE score and age and between the MMSE score and BMI. The results of the multivariate analysis of the six factors that may potentially affect propofol requirements are presented in Table 2. Only the BMI and the MMSE score affected the mean dose of propofol per minute.

All aspects of anaesthetic management were standardized. No premedication was used. A 18 G catheter was inserted in a forearm vein for fluid and drug administration. Non-invasive arterial pressure (MAP), ECG, oxygen saturation ($SpO_2$), and end-tidal CO$_2$ were monitored throughout the procedure.

Before general anaesthesia, femoral nerve block was given using 20 ml of ropivacaine 7.5 mg ml$^{-1}$. After 5 min of preoxygenation, anaesthesia was induced with etomidate 0.4 mg kg$^{-1}$ and sufentanil 0.3 μg kg$^{-1}$. The anaesthesia regimen using etomidate for induction and TCI propofol using the Schnider pharmacodynamic model for the maintenance of the hypnosis component of anaesthesia has been previously shown to provide cardiovascular stability and fast recovery, and therefore was safe in aged patients. Paralysis was achieved with cisatracurium 0.15 mg kg$^{-1}$. Laryngoscopy was attempted 5 min after the sufentanil administration and 5% lidocaine was applied topically on the glottis before tracheal intubation. The lungs of all patients were ventilated with a mixture of 50% oxygen and 50% air, and ventilation was adjusted to maintain $E_{CO_2}$ between 4.0 and 4.6 kPa. To monitor the depth of anaesthesia, bispectral index (BIS) (Aspect Medical System, MA, USA) was used. Baseline BIS of all patients was recorded before any injection of drugs. The initial target effect-site concentration of propofol was 0.5 μg ml$^{-1}$. Thereafter, propofol target concentration was adjusted to maintain BIS between the 40 and 60 range throughout the intraoperative period. The MAP was measured every 5 min. Hypotension, defined as an MAP of < 60 mm Hg or a decrease of > 30% from the baseline value lasting more than 1 min, was first treated by i.v. volume expansion (Ringer lactate or plasma substitutes). If hypotension was not successfully corrected, a bolus dose of ephedrine 6 mg was injected. Thirty minutes before the end of surgery, i.v. acetaminophen 1 g and nefopam 20 mg were given.

Data were analysed for 41 patients presented as mean (so). For each patient, we assessed the MMSE score, BMI, ASA classification, the total dose of propofol, and duration of its administration as indicated by the TCI device. The dependent variable was the mean value of propofol consumption calculated as the ratio of the total dose of propofol (mg) to the total duration of its administration (min). The independent factors for the dependent variable were examined using a multivariate analysis of variance (general linear model, stepwise multiple regression) using Systat 8.0 software. A value of $P < 0.05$ was considered significant.

### Results

The characteristics of the 41 subjects are shown in Table 1. For the cognitive performance, the mean MMSE score was 19 (7) before operation, and the mean total score on the HAMA was 6 (5) which reflects no or mild anxiety expressed by the patients.

The mean total dose of propofol administered and the mean duration of administration were 357 (204) mg and 65 (24) min, respectively.

<table>
<thead>
<tr>
<th>Number</th>
<th>$n=41$</th>
</tr>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>83 (65–99)</td>
</tr>
<tr>
<td>Sex ratio (M:F)</td>
<td>8:33</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60 (14)</td>
</tr>
<tr>
<td>Weight (range)</td>
<td>40–100</td>
</tr>
<tr>
<td>ASA classification</td>
<td>II/III 12/29</td>
</tr>
<tr>
<td>Hamilton anxiety rating scale</td>
<td>6 (5)</td>
</tr>
<tr>
<td>MMSE score</td>
<td>19 (7)</td>
</tr>
<tr>
<td>Body mass index (kg m$^{-2}$)</td>
<td>23 (4)</td>
</tr>
<tr>
<td>Body mass index (range)</td>
<td>16–36</td>
</tr>
<tr>
<td>Baseline BIS</td>
<td>91 (6)</td>
</tr>
<tr>
<td>Total dose of propofol administered (mg)</td>
<td>323 (205)</td>
</tr>
<tr>
<td>Total time of administration of propofol (min)</td>
<td>66 (24)</td>
</tr>
</tbody>
</table>
Table 2 Multivariate ANOVA (general linear model) of six factors with potential effect on propofol consumption (mg min\(^{-1}\)). BMI, body mass index; MMSE, mini-mental state examination.

<table>
<thead>
<tr>
<th>Propofol consumption</th>
<th>F(df,df)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>F(2,33)=2.49</td>
<td>0.09</td>
</tr>
<tr>
<td>Age</td>
<td>F(1,33)=0.004</td>
<td>0.95</td>
</tr>
<tr>
<td>BMI</td>
<td>F(1,33)=19.14</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Gender</td>
<td>F(1,33)=0.008</td>
<td>0.929</td>
</tr>
<tr>
<td>MMSE score</td>
<td>F(1,33)=14.49</td>
<td>0.001*</td>
</tr>
<tr>
<td>Duration of anaesthesia</td>
<td>F(1,33)=0.411</td>
<td>0.526</td>
</tr>
</tbody>
</table>

independent of the weight of the patients. The mean consumption of propofol per minute was 5.06 (2.15) mg min\(^{-1}\). A regression tree analysis of the two factors that affected the propofol requirements is presented in Figure 2. On the basis of BMI, two groups of patients were analysed. The mean dose of propofol was 4.08 (1.49) mg min\(^{-1}\) in patients with a BMI of < 22.94 and 6.73 (2.05) mg min\(^{-1}\) in patients with a BMI of > 22.94. Two subgroups of patients with a BMI of < 22.94 were further analysed. Patients with an MMSE of < 19 had a mean propofol dose of 3.13 mg min\(^{-1}\) and patients with an MMSE of > 19 needed 4.7 mg min\(^{-1}\) to maintain anaesthesia. The final tree contains three terminal nodes with a proportional reduction in error of 0.465, with a cut-off value for BMI at 22.94 and a cut-off value for MMSE at 19 (Fig. 2).

Using the cut value of the MMSE score, we divided the population of patients into two main groups (< 19 or ≥ 19) and performed regression analyses on the relationship between BMI and the mean consumption of propofol per minute (Fig. 3). Figure 3 shows the dose of propofol as a function of BMI for two groups of patients. There was a direct correlation between BMI and propofol requirements, i.e. an increase in BMI caused an increase in propofol dose. The absolute doses of propofol, however, were lower in patients with a lower cognitive function level.

Discussion

The present study shows, for the first time to our knowledge, that decline in preoperative cognitive status of patients, as assessed by MMSE, reduces the propofol requirement to maintain hypnosis in the elderly (patients more than 65 yr).

To adjust the propofol TCI, we maintained the BIS value between 40 and 60. We noticed that the mean preoperative BIS value was about 91 in our population of patients more than 65 yr, which is slightly lower than the value usually observed in younger patients (about 100). BIS was originally obtained from an algorithm based on the analysis of a large number of EEGs from volunteers and patients undergoing sedation and general anaesthesia with different agents.

Age-related EEG differences have been observed in the normal population and thus could influence the value of BIS. In this respect, demented patients have a significantly lower value of BIS than normal elderly controls. In our population of 41 patients, the preoperative BIS value appeared not to depend on either age or cognitive status as assessed here by preoperative MMSE (all \(P>0.05\)).

We observed that the propofol consumption during TCI depended on BMI, factor that is included in the internal pharmacokinetic model of Schnider used in this study. Indeed, the TCI propofol requirement is calculated using BMI. We could not prove any significant effect of age, and of gender, the population being about 80% of females in the present study. However, the adjustment of the TCI to the target depth of anaesthesia as assessed by BIS monitoring allowed us to reveal one more factor impacting on propofol consumption to maintain hypnosis in patients older than 65 yr: the level of preoperative cognitive status as assessed by the MMSE. In large epidemiological studies, the MMSE score is affected by ageing, but is considered as a co-dependent variable reflecting more precisely the brain ageing. Indeed, we did not observe any correlation between age and MMSE score in our limited population size examined here. However, our results showed clearly that the preoperative MMSE score influenced the mean propofol consumption as an additional factor, besides BMI.

The propofol consumption was more particularly decreased in patients with an MMSE score below 19 (Figs 2 and 3). As all our patients had an education ranging between 5 and 8 yr, it was not necessary to adjust individual values of MMSE to educational level. MMSE is a quick and simple tool to roughly assess the cognitive status and to classify elderly patients as no cognitive impairment (score range, 24–30), mild cognitive impairment (16–23), and severe cognitive impairment (below 15). However, the MMSE score observed in immediate preoperative period may not correspond exactly to the usual baseline MMSE score of the patient. Assessing manual skills is difficult in patients with complaints of pain. Moreover, the preoperative stress could...
influence the MMSE score. This is the reason why we excluded the patients with high levels of anxiety and/or high levels of pain from this study. However, a cut value of 19 is indicative of the presence of a preoperative cognitive impairment as a factor for decreasing the propofol requirement to maintain the hypnosis component of anaesthesia.

From our results, we cannot conclude whether the relationship between propofol requirement and MMSE score is due to differences in pharmacodynamics or pharmacokinetics, since no propofol concentrations were measured. However, a previous study by Schliebs and Arendt has shown a correlation between the MMSE score and the extent of the loss of cholinergic neurones in the basal forebrain in normal and pathological ageing in humans. Thus, the MMSE score appears to reflect the cerebral cholinergic dysfunction sustaining cognitive impairment. Propofol has an inhibitory effect on acetylcholine release, in a dose-dependent manner (more pronounced with a higher dose of propofol), in rodents. This depressant effect of propofol on cerebral acetylcholine release is observed in the frontal cortex and hippocampus. We previously demonstrated that the hypnotic potency of propofol was increased in animals with a prior cholinergic lesion in the cortex and hippocampus, produced by the intracerebral administration of a selective immunotoxin in rodents. From our previous results, brain sensitivity to propofol appears to have increased as soon as cholinergic transmission is altered. We suggest that a cognitive dysfunction linked to a cerebral cholinergic dysfunction might have influenced the brain pharmacodynamics of propofol in the present study. It is reasonable to suggest that less propofol may be needed in the presence of cognitive dysfunction. Thereby, the
dysfunctional brain is more sensitive to further reductions of cholinergic activity such as those caused by propofol. Such a concept could be important from a clinical point of view, as anaesthesia in elderly patients might need to take into account a putative brain sensitivity linked to ageing.

To conclude, our results show that the pre-existing cognitive status of the elderly significantly affected the propofol TCI requirement to maintain hypnosis, mainly the dose reduction of propofol in the presence of cognitive dysfunction. Given these results, we suggest that the clinical pre-operative evaluation of the cognitive status of the patient using MMSE could be an effective tool to improve the delivery of anaesthesia regimen in patients over 65 yr.

**Conflict of interest**

None declared.

**References**